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May 3, 2022

Radhika Fox
Assistant Administrator
Office of Water
US Environmental Protection Agency
1200 Pennsylvania Avenue, N.W., Mail Code 4101M
Washington, DC 20460

Re: Chemours Request for Correction of GenX Toxicity Assessment

Dear Assistant Administrator Fox:

We are six public health and environmental groups committed to protecting communities in Eastern North Carolina impacted by the extensive contamination of the Cape Fear River basin by Per- and Polyfluoroalkyl Substances (PFAS) released by Chemours' Fayetteville Works. Because of this contamination, over 500,000 residents consume drinking water containing numerous PFAS. These contaminants include the Hexafluoropropylene Oxide (HFPO) Dimer Acid and its ammonium salt, commonly referred to as GenX.

Our groups have long been concerned about the health threats of drinking-water exposure to GenX and other PFAS contaminating the Cape Fear River. In late 2020, we petitioned the Environmental Protection Agency (EPA) under the Toxic Substances Control Act (TSCA) to require Chemours to conduct health and environmental effects testing on 54 PFAS lacking critical data for protection of the health of communities.[1] GenX was included in this petition and the studies we recommended would have helped fill the serious data gaps now identified by EPA.

We are writing to express strong opposition to Chemours' March 18, 2022 request under the Information Quality Act (IQA) to withdraw and correct EPA's October 25, 2021 GenX Chemicals Toxicity Assessment. This EPA assessment was developed in a lengthy process with two rounds of peer review and a full opportunity for public comment. Its findings are meticulously documented and conform to EPA and National Academy of Sciences guidelines for chemical risk assessments. Chemours' IQA request adds nothing new to these scientific deliberations. Instead, it seeks to rehash issues that have already been fully vetted and carefully considered by EPA and its peer reviewers.

As acknowledged by Chemours,[2] the purpose of the IQA request is to delay an imminent EPA drinking water health advisory that would recommend reductions in GenX levels in drinking

[1] On December 28, 2021, EPA responded to the petition, concluding that petitioners had justified the need for testing but that it would not require almost all the studies that the petition requested.
[2] The IQA request states (pp. 33-34) that "EPA's health advisory should be based upon a revised assessment for HFPO-DA that addresses and corrects the procedural and scientific deficiencies noted

water which would protect against the risks of harm demonstrated by the assessment. EPA should reject this ploy to delay public health protection by denying the IQA request and issuing the advisory as soon as possible. This will immediately benefit our communities by enabling the State of North Carolina to compel Chemours to provide alternate water supplies to thousands of residents whose drinking water contains unsafe levels of GenX and other PFAS.

Significantly, on February 23, 2022, the Court of Justice of the European Communities issued a lengthy decision denying Chemours' challenge to the European Chemicals Agency's July 2019 listing of GenX as a "substance of very high concern." The Court rejected several of the scientific arguments made by Chemours in its IQA request.

Exposure to GenX in the Cape Fear Basin

GenX has been produced, initially as a byproduct and subsequently as an intentional product, by Chemours and its predecessor DuPont and discharged into the Cape Fear River for over four decades. For most of that period, GenX was a byproduct in the production of vinyl ethers. After Chemours submitted premanufacture notices for GenX under the Toxic Substances Control Act in 2008, DuPont began commercial production of GenX, touting it as a "sustainable replacement" for perfluorooctanoic acid (PFOA), which was being phased out as a processing aid in the manufacture of fluoropolymers.

As described (pp. 3-4) in the EPA assessment, GenX has been consistently detected in source water and finished drinking water, as well as in private wells, throughout communities near and downstream of the Fayetteville plant. Conventional and advanced water treatment processes in use in the Cape Fear basin have shown limited effectiveness in reducing GenX levels in finished drinking water. Exposure to GenX and other PFAS derives not only from drinking water but from other pathways, including air emissions, rainwater, and locally grown food.[3] The health effects of GenX are likely additive to or synergistic with several other Chemours-produced PFAS found in the drinking water and blood of Cape Fear residents.[4]

Findings of the GenX Toxicity Assessment

The final GenX toxicity assessment reinforces our longstanding concerns about the risks of historical and ongoing exposure to GenX in Cape Fear communities. The EPA assessment

herein and incorporates the results of the in vitro study and liver pathology research. The health advisory should not be undertaken until after a revised assessment can be peer reviewed."

[3] The EPA assessment indicates (p. 28) that intake of GenX by Cape Fear residents "is expected to occur by dermal exposure (i.e., contact of exposed parts of the body with water containing GenX chemicals during bathing or showering, and dishwashing) and inhalation exposure (e.g., volatilization of the GenX chemicals from the water during bathing or showering, or while using a humidifier or vaporizer" or as a result of air emissions from the Chemours facility.

[4] For example, in 2019, North Carolina State University's Center for Human Health and the Environment collected samples of water from 84 private wells and blood from 153 community members in Cumberland and Bladen Counties near the Fayetteville plant. The samples were analyzed for 26 PFAS. In May of 2020, the Center released the results of the private well sampling. Eleven PFAS, including GenX, were found in over 50 percent of the wells.

concludes that GenX causes adverse effects on the liver, kidneys, immune system and development of offspring, and is associated with an increased risk of cancer. It sets a Reference Dose (RfD) of 3×10^{-6} mg/kg/day for chronic exposure. This RfD represents the daily exposure to GenX that is likely without appreciable risk to humans over a lifetime. Since North Carolina residents have been ingesting GenX in drinking water continuously for several decades, exposure above the RfD poses a serious health risk to Cape Fear communities. Indeed, the RfD likely understates this risk because it does not account for exposure to at least 350 other PFAS in the region's drinking water and how GenX might interact with them in the human body and our environment, nor does it account for other pathways of exposure to GenX.

Recent monitoring data show that GenX levels in many samples of drinking water near and downstream of the Chemours plant and in personal drinking water wells result in exposure *above the RfD.*[5] Thus, Eastern North Carolina residents are now ingesting GenX at concentrations *determined to be harmful by EPA*.

EPA GenX Drinking Water Advisory

Recognizing the urgency of reducing GenX exposure in drinking water, EPA has announced that it will issue a GenX drinking water health advisory in the Spring of 2022. A consent order between Chemours and North Carolina Department of Environmental Quality (NCDEQ) requires the company to provide permanent replacement drinking water supplies to any owner of a private well "contaminated by concentrations of GenX compounds in excess of . . . *any applicable health advisory*" (emphasis added). On November 3, 2021, NCDEQ put Chemours on notice of the need to revise its Drinking Water Compliance Plan under the consent order in accordance with EPA's RfD once the drinking water advisory is issued. Thus, prompt issuance of the advisory will trigger Chemours' obligation to provide alternate water supplies to owners of wells with GenX contamination that exceeds the RfD. A delay in issuing the advisory while EPA considers Chemours' unwarranted IQA request would relieve the company from meeting this obligation, perhaps for years, continuing to expose residents to unsafe GenX contamination.

Development of the GenX Toxicity Assessment

EPA released its draft toxicity assessment for GenX in November 2018. It accepted public comments on the draft for 60 days, from November 21, 2018 to January 22, 2019. Along with many stakeholders and experts, Chemours and its scientific consultants submitted extensive comments. Five independent external peer reviewers reviewed the draft assessment, responding in

[5] In 2018, the North Carolina Department of Health and Human Services (NCDHHS) set a preliminary health goal for GenX of 140 ppt. The goal was based on an RfD of 0.0001 mg/kg/day and assumed drinking water intake for bottle-fed infants and a relative source contribution of 20% to account for potential exposure to GenX chemicals from other media and routes. The new EPA RfD is 3% of the RfD used by NCDHHS. Using the same assumptions made in calculating the NC preliminary health goal, a "safe" drinking water level based on the EPA RfD would therefore be 4.2 ppt. Recent GenX levels in finished drinking water as measured by the Cape Fear Public Utility Authority and Brunswick County Public Utilities have ranged between 3-16 ppt. For comparison, these utilities measured total PFAS levels in finished water of 93 and 94 ppt in early March 2022. Monitoring of private wells in the Fayetteville area in 2019 by the GenX Exposure Project showed a median GenX concentration of 103 ppt.

writing to eight detailed charge questions. The reviewers were strongly supportive of the EPA draft. EPA convened a supplemental seven member peer-review panel in the spring of 2021 to address new information received since the initial comment period, including the results of a National Toxicology Program (NTP) Pathology Working Group (PWG) review and recent reproductive/developmental toxicity data raising concern about impacts of GenX on pregnancy. EPA posed five charge questions to the supplemental review panel, which, as before, provided detailed written responses. Again, the reviewers were supportive of EPA's approach and none raised major concerns about the draft final assessment.

When EPA finalized the assessment in November 2021, it released a 69 page document fully responding to each of the public comments, including those submitted by Chemours and its consultants. A review of the comments demonstrates that numerous independent scientists, states, and other organizations called for *strengthening* EPA's draft assessment, a path that EPA ultimately followed. In addition to addressing public comments, EPA issued reports presenting and responding to the recommendations and feedback of the initial and supplemental peer review panels. These documents demonstrate the care and thoroughness with which the Agency considered the input of stakeholders, including Chemours, and external scientists.

Lack of Scientific Support for Chemours' Criticisms of the EPA Assessment

The alleged "flaws" in the EPA assessment identified in the Chemours' IQA request include (pp. 3-4) the following:

- The rodent liver effects underpinning the assessment are peroxisome proliferator-activated receptor alpha (PPAR-alpha) effects that are not relevant to humans;
- The assessment relies on observations by the National Toxicology Program Pathology Working Group (NTP PWG) that do not follow evaluation criteria set forth in the peer-reviewed scientific literature;
- The assessment uses inappropriate and significantly inflated uncertainty factors that are inconsistent with EPA's own guidance and practice in other toxicity assessments;
- EPA has not taken into account available epidemiological evidence showing no increased risk of cancers or liver disease attributable to exposure to GenX.

As shown below, with the strong support of the peer reviewers, EPA fully addressed these issues in its final assessment and supporting materials, explaining the scientific justification for its approach and responding to commenters, including Chemours and its consultants, who made arguments that now form the basis for the IQA request.

Relevance of PPAR-alpha Liver Effects to Humans

From the outset of the assessment process, EPA highlighted this issue and asked for feedback from its external reviewers and stakeholders. Thus, its charge to the first peer review panel posed the following question (p.10):

The draft assessment for GenX chemicals identifies liver effects as a potential human hazard. EPA evaluated the available evidence for liver effects, including the potential role of PPARα, using Hall et al. (2012) criteria for adversity.

a. Please comment on whether the available data have been clearly and appropriately synthesized for these toxicological effects.
b. Please comment on whether the weight of evidence for hazard identification has been clearly described and scientifically justified.
c. Please comment on whether the conclusions regarding adversity are scientifically supported and clearly described.

The reviewers generally responded that the weight of evidence for adverse liver effects was supported by the data, clearly described and scientifically justified. None advised EPA that liver effects were irrelevant to humans because of the PPAR-alpha mechanism.

EPA's final toxicity assessment devotes several pages (pp. xii, 82-86) to the Mode of Action (MOA) for liver effects, concluding that "the constellation of liver lesions observed in the rodent are relevant to human health and not a result of PPARα-induced cell proliferation unique to rodents." In support of this conclusion, EPA determined (pp. 84. 86) that:

> *Although there is evidence for a PPARα MOA in the liver, particularly in the high-dose groups in the available studies, data indicate that liver toxicity extends beyond a single PPARα-based MOA*. For example, liver necrosis was consistently observed in rodent toxicity studies with HFPO dimer acid ammonium salt and was reaffirmed by the NTP PWG's review of the 90-day subchronic study in mice and the reproductive and developmental toxicity study in mice (appendix D), which suggests that cytotoxicity is also a possible MOA (emphasis added).
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> *Taken together, the available data indicate that a PPARα MOA is plausible in the liver in response to GenX chemical exposure, especially at doses greater than 0.5 mg/kg/day; however, there are not yet enough data to conclude that PPARα activation is the sole mechanism underlying the liver effects associated with exposure to GenX chemicals.* For example, there are no studies investigating GenX chemical exposure in PPARα-null mice. It is worth noting that exposure to PFOA has been demonstrated to induce liver effects in PPARα-null mice, including hepatocellular hypertrophy (Minata et al., 2010). *Additionally, available studies indicate that other MOAs (e.g., PPARγ, mitochondrial dysfunction, and cytotoxicity) are also plausible.* The data are not adequate to conclude that any of the MOAs described here are the sole toxicologic MOA for HFPO dimer acid and/or ammonium salt in the liver and especially in other organ systems (emphasis added).

EPA also explained (p. 86) why, despite the possible role of PPARα receptors, the liver effects on which its RfD were based were indicative of potential toxicity in humans:

> Because liver effects such as increases in liver weight and hepatocellular hypertrophy (also referenced here as cytoplasmic alteration per NTP PWG's review) can be associated with activation of cellular PPARα receptors, EPA evaluated observed liver effects

> resulting from HFPO dimer acid ammonium salt exposure against the Hall criteria (Hall et al., 2012). These criteria indicate that increased liver weight and hepatocellular hypertrophy must be accompanied by histologic or clinical pathology indicative of liver toxicity to be considered adverse. Histologic or clinical pathology indicative of liver toxicity can include changes in liver enzyme concentrations in the serum, necrosis, inflammation, and degeneration. *With these criteria in mind, EPA concluded that some of the observed liver effects such as single-cell and focal necrosis, increased apoptosis, and increases in serum liver enzymes indicate toxicity of relevance to humans as opposed to PPARα-induced cell proliferation unique to rodents* (emphasis added).

In its response to comments document, EPA directly addressed (p.36) the assertions of Chemours' consultants – repeated in the IQA request – that the liver effects should be discounted as irrelevant to humans because of a PPARα MOA:

> EPA describes the data supporting activation of the peroxisome proliferator-activated receptor pathways in detail in section 6.0 (EPA, 2021a). EPA has revised the document to indicate that, at this time, the findings regarding the MOA are not adequate to conclude that a PPARα MOA is solely operative for HFPO dimer acid and/or ammonium salt. Contrary to the commenter's assertion, there is uncertainty about the MOA(s) for GenX chemicals even though some of the available data are consistent with a peroxisome proliferation MOA.

In short, Chemours' claims were exhaustively addressed during the toxicity assessment process and further consideration of these claims would serve no purpose except delay.

National Toxicology Program Pathology Working Group

DuPont scientists who originally reviewed the liver pathology slides from the two critical studies conducted by the company determined that GenX caused necrosis and apoptosis, consistent with a non-PPARα MOA. Seeking to challenge these findings, Chemours and its experts commissioned a reanalysis by a consulting pathologist of the slides which purported to show that, for both studies, apoptosis was the primary adverse effect of note in the liver. To resolve these conflicting interpretations, EPA took the unusual step of requesting that NTP convene a PWG to provide an independent, expert review of selected tissues from the two studies.

Known as the gold standard in the scientific community, NTP PWG reviews are a rigorous process in which a team of pathologists collaborate to reach a consensus on the classification of reported effects using standardized and broadly accepted diagnostic criteria. As EPA summarized the work of the GenX PWG in its response to comments (p. 12):

> As part of this PWG, one pathologist reviewed all the slides from the two studies that Du Pont submitted to EPA and classified liver cell death according to the INHAND Organ Working Group's diagnostic criteria, which describe how pathologists can distinguish between apoptosis and single-cell necrosis in standard H&E-stained tissue sections (Elmore et al., 2016). Other liver effects were classified according to the INHAND document containing standardized terminology effects were classified according to the

> INHAND document containing standardized terminology of the liver (Thoolen et al., 2010). The PWG coordinator then confirmed the classifications and selected example slides representative of the observed liver effects for review by the other six members of the group . . . There was majority agreement on all reviewed lesions. The PWG consensus opinion for each slide, including any additional diagnoses made by the PWG panel, was recorded and presented in the final PWG report.

According to the response to comments (pp. 12-13), the PWG "confirmed single-cell necrosis and focal necrosis in the mid- and high-dose groups of both studies" and found that these effects exhibited a dose-response relationship. "Findings of apoptosis were observed but limited to the highest dose groups in both sexes in both studies." Thus, the "PWG results confirm the conclusions presented in" the original DuPont studies "that the observed liver lesions, which include single-cell necrosis, are treatment-related adverse effects." EPA shared the results of the PWG report with the supplemental peer review panel, which agreed that the constellation of liver effects identified by the PWG provided a sound basis for EPA's determination of subchronic and chronic RfDs.

There have now been four pathology reviews of the two DuPont studies. The rigorous and definitive PWG analysis rejects the reviews performed for Chemours, reaffirms the original DuPont findings and supports EPA's RfDs. Chemours may not like this outcome but has identified no credible reason to revisit it.

Uncertainty Factors

Long-standing EPA practice in developing RfDs is to apply Uncertainty Factors (UFs) to account for limitations and gaps in the available data and the possibility that further testing would identify additional end-points of concern or known adverse effects at lower doses. EPA issued detailed guidance for selecting UFs in 2002 and has followed this guidance in numerous assessments. In the final GenX toxicity assessment, EPA relied on the guidance to calculate five separate UFs which, when combined, resulted in a total UF of 3000 for determining a chronic RfD. The assessment (pp. 92-97) explains the basis for each UF in detail. Chemours claims, however, that "[b]etween EPA's draft and final Toxicity Assessment, the total uncertainty factors increased exponentially (from 300 to 3000), notwithstanding that the final Toxicity Assessment incorporates *additional* data and studies (and thus, in truth, there is less, not more, uncertainty) (emphasis in original)" (p.25). Chemours' reasoning does not stand up to scrutiny.

EPA's charge to the supplemental peer review panel (pp. 3-4) fully explained why two of the UFs were increased from 3 to 10 in the final assessment:

> EPA has identified new toxicological and toxicokinetic information published since the last peer review of this document that demonstrate accumulation of GenX chemicals in the whole embryo and identified additional adverse effects that EPA had not considered in applying a database uncertainty factor of 3. Based on this new information, EPA has increased the uncertainty factor to 10 to address database limitations on the impact of GenX chemicals exposure specifically on reproduction and development.

> Because a 2-year chronic mouse study is unavailable, the impact of a longer dosing duration on both the incidence and severity of liver effects in mice is unknown. This is important because the new analysis by NTP indicates that the duration of exposure appears to play a larger role than previously understood in the progression and severity of liver effects resulting from GenX chemical exposure, as evidenced in female rats. . . .[A] 2-year chronic study in the mouse would provide information critical to understand the progression of these liver effects. Specifically, it is possible that a longer duration study would result in an increased frequency and/or magnitude of response and could also reveal additional adverse effects at lower doses than currently observed in the existing less-than-chronic mouse studies.

The supplemental peer reviewers were fully supportive of increasing the two UFs, as the responses of Dr. Elaine Faustman of the University of Washington (pp. 16, 21) illustrate:

> This reviewer agrees with the conclusion of the internal draft that in fact, the uncertainty has increased. This should not be surprising given the intensity of investigation of the perflorinated compounds and the expanded portfolio of endpoints that are being revealed. The internal report identifies additional uncertainties in observations in immune response, molecular responses that appear to be beyond PPAR alpha dependent responses and which identify further concerns regarding developmental sensitivity and kinetics. Since the uncertainties have now been expanded and cover both kinetic and dynamic considerations, the increase of the uncertainty factor from 3 to 10 is appropriate.
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> This reviewer agrees with a selection of uncertainty factor of 10 to account for extrapolation from a subchronic to a chronic exposure duration. Detailed support for this number is provided by EPA and includes the following considerations: complexity of kinetics especially over time and lifestage, clarification of the adversity of the hepatic alterations observed in the Dupont study used for the critical effect (see the NTP re-assessment and use of the most current pathology classification guidance) that now highlight more concern over the long term manifestations of these adverse impacts in the hepatic system, further identification of cholesterol changes and concerns over adiposity and chronic health impacts and dose response for these complex endpoints across sex and time.

While Chemours touts (p. 25) the large "number of toxicity studies and amount of toxicity data available" on GenX, the EPA assessment presents a very different picture: it enumerates the many gaps in the GenX data-base that create large uncertainties about the range and severity of its adverse effects and require substantial UFs to assure that the RfD is adequately protective of exposed communities. (Attachment 1 lists these data-gaps.) Because Chemours could have reduced these uncertainties by investing in more testing but failed to do so, it has no standing to complain about EPA's UFs.

"Negative" Epidemiology Studies

Claiming that "[t]he flaws in EPA's HFPO-DA Toxicity Assessment are further corroborated by real-world epidemiological data," Chemours' IQA request faults EPA (p. 30) for failing to

consider 2017 data from NCDHHS purporting to show that "rates of liver and other cancers are *generally lower* in North Carolina counties with exposures to [GenX] than the rates reported in the U.S. general population, in the state of North Carolina, and in North Carolina counties without alleged exposure to [GenX]" (emphasis in original).

The data Chemours cites is merely a tabulation of cancer incidence data in different North Carolina counties. This tabulation is not an epidemiological study and was not published in the peer reviewed literature. Moreover, according to NCDHHS itself, Chemours' description of the data is simply incorrect. As reported in a recent article in *The Intercept:*

> NCDHHS did not conclude that rates of liver and other cancers are generally lower in North Carolina counties with exposures to [GenX] than the rates reported in the U.S. general population, in the state of North Carolina, or in North Carolina counties without alleged exposure" to GenX, Catie Armstrong, a spokesperson for the department, wrote in an email to The Intercept. Armstrong also noted that while overall cancer rates in the four counties studied were similar, in New Hanover County rates of testicular cancer were elevated over a 20-year period and rates of liver cancer were higher over a five-year period. The cancer rates collected by the health department are descriptive, Armstrong said, and "only a comprehensive research study can provide information about whether a specific exposure might be associated with increased rates of cancer.

The EPA toxicity assessment (p. 95) emphasizes that, in addition to other data gaps, "there are no human toxicity data from epidemiological studies in the general population or worker cohorts evaluating the health effects of exposure to these GenX chemicals." Although based on limited and incomplete information, NCDHSS's finding of elevated testicular and liver tumors in New Hanover County is cause for concern and underscores the need for a comprehensive epidemiology study of Cape Fear communities. Our TSCA testing petition sought to require Chemours to fund such a study but the TSCA program – unjustifiably in our view -- has refused to impose this requirement.[6] As epidemiology plays a critical role in recent EPA toxicity assessments to support drinking water standards for PFOS and PFOA, the importance of developing robust human data on GenX and other PFAS in North Carolina drinking water has become even more compelling.

In sum, the Chemours' IQA request to withdraw and correct the EPA GenX toxicity assessment is lacking in scientific merit. EPA should promptly deny the request and issue the GenX drinking water health advisory as soon as possible to provide enhanced protection to at risk Cape Fear communities.

If you have any questions about the letter, please contact our counsel Bob Sussman at bobsussman1@comcast.net or 202-716-0118.

[6] The petition response cites two limited and inadequate studies underway in North Carolina and ATSDR studies being conducted in other areas of the country focusing mainly on PFAS in fire-fighting foam, not GenX and other PFAS found in drinking water and human blood in Cape Fear communities. As EPA's recent toxicity assessments indicate, epidemiological data are meaningful only where the population studied was exposed to the compounds of interest – in this case, GenX and other PFAS manufactured by Chemours.

Respectfully submitted,

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ATTACHMENT 1 – DATA GAPS IDENTIFIED IN EPA GENX TOXICITY ASSESSMENT

"Because the mouse presents with liver necrosis at much lower doses and shorter durations (0.5 mg/kg/day at 53–85 days) than the rat and because the mode of action for these liver effects is uncertain (see section 6), it is critical to have a 2-year chronic study in the mouse to understand the progression of these liver effects." (p.93)

"[W]hen evaluating the available endpoints and studies to ensure comprehensive characterization of the potential toxicity, there are important deficiencies that need to be considered, particularly for understanding developmental toxicity. . . . For GenX chemicals, there are reproductive or developmental effects of concern in mice . . . that have not been studied yet." (p.93)

"[O]ther database deficiencies include the absence of a full two-generation reproductive and developmental toxicity study to understand if latent effects occur as a result of exposure to GenX chemicals during development (e.g., adverse cardiometabolic outcomes in adult offspring associated with placental insufficiency). . . . These effects . . .highlight the importance of having a full two-generation reproductive and developmental toxicity study." (p. 94-95)

"[O]ther database gaps are noted for GenX chemicals with respect to potential immune, hematological and neurological effects."(p.95)

"Additionally, there are no human toxicity data from epidemiological studies in the general population or worker cohorts evaluating the health effects of exposure to theseGenX chemicals." (p. 95)

"The combined GenX chemicals immunotoxicity dataset was found to be incomplete as it did not include sufficient measures of immunopathology, humoral immunity, cell- mediated immunity, nonspecific immunity, or host resistance, but the available studies are suggestive of a potential immune hazard. Data on the potential for these GenX chemicals to impact aspects of immune function beyond immunosuppression are lacking. Additional studies, therefore, would be useful to support a more conclusive determination of immunotoxic potential." (p. 95)

"The potential neurodevelopmental effects that might result from the disruption of these thyroid hormones are unknown and require additional investigation at lower doses." (p. 96)

"Given the evidence that the liver is the target organ for toxicity and the primary organ for tumor development, additional research is needed using chronic duration exposures in mice." (p. 103).

“Data for the elucidation of differential susceptibility dependent on life stage (e.g., developing embryo/fetus, women of reproductive age, or pregnant women) are not available. . . . No human toxicity or epidemiological studies are available in the literature that address early developmental or reproductive life stage.” (p. 10